ARTICLE

Managing osteoarthritis

SUMMARY

Management of osteoarthritis should be based on a combination of non-drug and drug treatments targeted towards prevention, modifying risk and disease progression.

Obesity is the most important modifiable risk factor, so losing weight in addition to land- and water-based exercise and strength training is important.

While paracetamol can be tried, guidelines recommend non-steroidal anti-inflammatory drugs as first-line treatment for osteoarthritis. If there are concerns about the adverse effects of oral treatment, particularly in older patients or those with comorbidities, topical non-steroidal anti-inflammatory drugs can be used.

Glucosamine does not appear to be any better than placebo for pain. Its effect on the structural progression of disease when taken alone or in combination with chondroitin is uncertain. Fish oil has not been found to reduce the structural progression of knee arthritis.

Surgical interventions should be avoided in the first instance, with arthroscopic procedures not showing benefit over sham procedures or optimised physical and medical therapy. Joint replacement surgery should be considered for severe osteoarthritis.

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Introduction

Osteoarthritis is a heterogeneous disease characterised by failure of the synovial joint including loss of articular cartilage, osteophyte formation, meniscal damage, ligamentous laxity and subchondral bone changes.[1] It is a chronic condition resulting from the interaction of multiple factors including genetic, metabolic, biochemical and biomechanical. Obesity is the single most important risk factor for knee osteoarthritis over other factors such as joint injury or genetic predisposition.

The management of osteoarthritis has shifted from the traditional approach of pain control to include interventions to improve tolerance for functional activity and quality of life. Optimal management involves non-drug and drug approaches that focus on preventing disease and stopping progression, as opposed to just targeting palliation of disease.[2]

Non-pharmacological management

After managing the pain, core interventions for all patients with osteoarthritis, with or without comorbidities, are land-based exercise, weight management, strength training, water-based exercise, self-management and education.[3] Exercise is universally recommended by clinical guidelines, and should be individualised after patient assessment. Meta-analyses have shown exercise to have small to moderate effect sizes for improved function and pain relief, similar to those achieved with non-steroidal anti-inflammatory drugs (NSAIDs) and analgesia.[4] Targeted muscle strengthening and general aerobic exercises are recommended, with water-based exercises suggested for those with functional and mobility limitations.[1,5] Stretching and flexibility exercises generally form part of an overall exercise program for osteoarthritis, to maintain or increase the range of motion in the joints. Supervised group or individual exercise is superior to independent home exercise for pain reduction.[6]

Mobility aids such as a stick (used in the opposite hand), knee braces and foot orthoses can also diminish pain and improve function.[7-9]

Obesity is the single most important modifiable risk factor.[2,10] A meta-analysis found that a 5% decrease in weight within a 20-week period is beneficial for knee osteoarthritis.[11] A more recent trial showed up to a 50% improvement in symptoms with 10% weight reduction through diet and exercise.[12]

NSAIDs

NSAIDs are often considered to be the preferred first-line drug treatment for osteoarthritis. They have shown efficacy similar and superior to paracetamol.[13,14] Systematic reviews have found that NSAIDs are superior for rest pain and overall pain.[15]

The potential adverse effects of routine NSAID use are well documented. Gastrointestinal toxicity causes over 16 500 deaths and hospital admissions per year in the USA.[16] Associated cardiovascular[17] and

renal risks are also a concern. These risks pertain to both non-selective and cyclo-oxygenase (COX-2)-selective NSAIDs, even though COX-2 inhibitors have a better safety profile. A meta-analysis of 26 studies comparing the two found that COX-2 inhibitors reduced the relative risk of dyspepsia by 12% and the absolute risk by 3.7%.[18] Other systematic reviews confirm similar findings.[19]

The concomitant use of proton pump inhibitors with NSAIDs is generally recommended in patients with associated comorbidity risks. The same meta-analysis found that combining an NSAID with a proton pump inhibitor reduced the relative risk of dyspepsia by 66% and the absolute risk by 9% compared with an NSAID alone.[18]

The optimum duration of NSAID therapy is unclear. A meta-analysis of randomised trials[19] found no clear association between the duration of therapy with selective or non-selective NSAIDs and the risk of cardiovascular events. One small trial found continuous celecoxib use to be slightly more effective than intermittent use on pain and function, with similar rates of withdrawals due to adverse events.[20] No trials have been designed to assess serious gastrointestinal or cardiovascular harms associated with intermittent dosing strategies.

Paracetamol

Because of the adverse effect profile of NSAIDs, paracetamol (up to 4 g/day) has been the general analgesic of choice for mild to moderate pain in osteoarthritis for many practitioners. However, it is no longer recommended as first line by osteoarthritis guidelines.[3,21] A meta-analysis found low-level effects of paracetamol for pain management in osteoarthritis,[3,22] and a randomised controlled trial found paracetamol 4 g/day was no better than placebo for knee osteoarthritis.[23] In addition, increased safety concerns with paracetamol are arising, especially for patients with comorbidities. A 2012 review found an increased risk of gastrointestinal events and multi-organ failure with supratherapeutic doses, which are often taken for chronic pain.[24] Also, an analysis from the large prospective Nurses' Health Study found heavy use of paracetamol (>22 days/month) is associated with an increased risk of cardiovascular events (RR* 1.4, 95% CI† 1.1–1.6) similar to that with heavy use of NSAIDs (RR 1.4, 95% CI 1.3–1.6).[25]

Furthermore, there are concerns regarding gastrointestinal blood loss with concomitant use of NSAIDs and paracetamol. One study found the risk of gastrointestinal-related hospitalisation was higher with combination treatment (HR‡ 2.55, 95% CI 1.98–3.28) compared with paracetamol alone (>3 g/day) (HR 1.20, 95% CI 1.03–1.40) and NSAIDs alone (HR 1.63, 95% CI 1.44–1.85).[26]

Topical therapies

The benefits of both topical NSAIDs and capsaicin are achieved through regular use, with recommended application of 3–4 times/day. There are associated local adverse effects including rash, burning and itching.

NSAIDs

Topical NSAIDs are appropriate for both knee and hand osteoarthritis as local drug delivery reduces gastrointestinal adverse reactions.[27,28] Efficacy is greater than placebo and comparable to oral NSAIDs.[28] Multiple formulations have been trialled including topical ketoprofen[29] and diclofenac sodium 1.5% topical solution in dimethyl sulfoxide.[27]

Safety with diclofenac sodium 1% gel has also been shown in the older population in a 12-month, post hoc analysis of patients with knee osteoarthritis. The overall rates of cardiovascular and gastrointestinal adverse events were similar for people under and over 65 years of age.[30]

To date, most studies have focused on individuals with knee-only osteoarthritis so the benefits of topical NSAIDs on people with multiple-joint osteoarthritis remain uncertain. Despite this, topical NSAIDs are increasingly being considered as a first-line pharmacological option, especially in patients with an increased risk of adverse events.

Capsaicin

Topical capsaicin can be used as an alternative or as an adjunct to standard drug treatment. Reviews of randomised controlled trials found that topical capsaicin is superior to placebo for knee osteoarthritis and reduces pain by 50%.[19,31] In general, a concentration of 0.025% capsaicin was better tolerated than 0.075%. Withdrawal because of an adverse event was more common with capsaicin than with placebo (13% vs 3%).[31]

Intra-articular injections

Intra-articular corticosteroid injections provide short-term pain relief (1–2 weeks in randomised controlled trials) and improved function for patients with osteoarthritis. They can be considered in patients who present with acute exacerbations with joint effusions and local inflammation. However, intra-

* RR relative risk

† CI confidence interval

‡ HR hazard ratio

articular injections given more frequently than once every four months can result in cartilage and joint damage,[32,33] as well as increased risk of infection.

The benefit of intra-articular hyaluronic acid injections is uncertain with inconsistent findings seen in meta-analyses. Trials showing benefit found varying effect sizes. A recent sensitivity analysis assessing blinded trials found only a small beneficial effect on pain.[34] The efficacy of corticosteroids is more significant than intra-articular hyaluronic acid in the short term. However in another comparison, hyaluronic acid provided longer-lasting benefit, extending beyond eight weeks.[35]

Opioids

Opioids are an alternative for patients who cannot tolerate or be prescribed first-line drugs because of contraindications due to comorbidities. Overall, systematic reviews concluded that oral and transdermal opioids were more effective compared to placebo in relieving pain and improving function in patients with hip and knee osteoarthritis. Benefits were small to moderate and adverse events caused many patients to withdraw. The usefulness of opioids in the long term is limited.[36]

Opioids have an increased risk of adverse events when compared with NSAIDs, including fractures (HR 4.47, 95% CI 3.12–6.41), cardiovascular events (HR 1.77, 95% CI 1.39–2.24) and all-cause mortality (HR 1.87, 95% CI 1.39–2.53).[37] When compared with placebo, patients were four times more likely to discontinue opioids due to an adverse event (RR 4.05, 95% CI 3.06–5.38).[36]

Duloxetine

The pain experienced in osteoarthritis is multifactorial. Often coexistent depression and neuropathic pain compound the overall pain syndrome. There is increased interest in centrally acting drugs such as selective noradrenaline and serotonin reuptake inhibitors. In a comparative trial, more people taking duloxetine reported reduced pain (by at least 30%) than those taking placebo (65% vs 44%).[38] Duloxetine can be a potential adjunct to conventional osteoarthritis treatment as additional pain reduction and improvement in function is seen when it is added to oral NSAIDs compared to placebo. Common adverse effects of duloxetine include nausea, constipation, fatigue, dry mouth and decreased appetite.[39]

Surgery

Joint replacement surgery should be considered for severe clinical disease with inadequate response to conservative treatment. Arthroscopic procedures for knee osteoarthritis have not provided additional benefit in people receiving physical and medical therapy.[40,41]

Complementary medicines

The most commonly used alternative treatment for osteoarthritis is glucosamine. In randomised controlled trials, it has a similar effect to placebo for pain, with independent trials showing smaller effects than commercially funded trials.[4] The Glucosamine/Chondroitin Arthritis Intervention Trial, a US National Institutes of Health-funded study, found that glucosamine was not significantly better than placebo in reducing knee pain (by 20%).[42] Evidence remains controversial regarding a possible structure-modifying effect (slowing or halting the progression of cartilage loss and other structural changes in the joint).

Similarly with chondroitin, its effect on symptomatic relief is uncertain – some reviews find an effect while others show no significant benefit over placebo.[43,44] Its ability to modify disease is also variable. Some studies found a reduction in the rate of decline in joint space width (0.07 mm/year, 95% CI 0.03–0.10).[45] Another trial found a statistically significant reduction in joint space narrowing after two years for a glucosamine/chondroitin combination compared to placebo. However, no statistical difference was found with individual treatment alone.[46]

Fish oil use is gaining popularity for osteoarthritis. While there are some trials in rheumatoid arthritis, its use in osteoarthritis remains uncertain. The components eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduced expression of degradative enzymes and inflammatory cytokines in in vitro cartilage models of osteoarthritis.[47,48] However, in a clinical study fish oil did not retard structural progression of symptomatic knee osteoarthritis at low or high doses.[49]

Newer therapies for osteoarthritis

There are numerous drug treatments for osteoarthritis, however their efficacy and adverse effect profiles often limit their use. At present there is no proven structure-modifying therapy available. The focus in osteoarthritis research is now shifting towards targeted biological therapies used in rheumatoid arthritis. As chronic forms of osteoarthritis are considered to be 'low' inflammatory conditions, research is underway into biological therapies targeting angiogenic factors, cytokines and pro-inflammatory mediators.

Different drugs targeting bone remodelling, including bisphosphonates and strontium ranelate, are also under investigation. Strontium ranelate reduced pain

and radiological progression in randomised controlled trials.[50,51] However, in light of emerging data on cardiovascular risks, the potential benefits may not be justifiable.[52]

Commercial stem cell therapies have recently emerged for knee osteoarthritis. To date, there is no supportive evidence to advocate these treatments. Both the International Society for Stem Cell Research and Australian Rheumatology Association are against their current use for osteoarthritis.

Developing novel therapies for osteoarthritis is not without its challenges. Newer analgesics such as tanezumab, a nerve growth factor inhibitor, showed promise for improving pain and function in hip and knee osteoarthritis. However, the trials were halted after a small number of patients developed rapid joint destruction.[53]

Conclusion

There is a need for better therapeutic interventions for osteoarthritis. In the meantime, the management of osteoarthritis should be multifaceted, including non-drug interventions aiming at preventing disease and slowing its progression. If required, choosing optimal analgesia for an individual requires careful consideration and discussion regarding the relevant trade-offs.

David Hunter is an author on the Osteoarthritis Research Society International (OARSI) guidelines.

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